RESEARCH COMMUNICATION

Genetic Polymorphisms of Methylenetetrahydrofolate Reductase and Susceptibility to Colorectal Cancer

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Abstract

Objectives: To study the relation between genetic polymorphisms of methylenetetrahydrofolate reductase (MTHFR) C677T or A1298C and the susceptibility of colorectal cancer. Methods: We conducted a case-control study with 315 cases of colorectal cancer and 371 population-based controls in Jiangsu province, China. The epidemiological data were collected, and DNA of peripheral blood leukocytes was obtained from all of the subjects. MTHFR C677T and A1298C genotypes were detected by PCR-RFLP method. Results: (1) When men and women were assessed together, the frequencies of the MTHFR C677T and A1298 genotypes or their alleles were not significantly different between controls and colon cancer or rectal cancer cases. No significant relation was observed between MTHFR C677T or A1298C polymorphisms and colon or rectal cancer susceptibility. (2) Among males, individuals who had MTHFR C677T T/T genotype were at a significantly higher risk of developing colon cancer (age-, residence-, smoking, alcohol drinking-, tea consumption-adjusted OR=2.15, 95%CI: 1.07-4.33) compared with those who had C677T C allele. Individuals who had C677T T/T and A1298C A/A genotypes were at an increased risk of developing colon cancer (adjusted OR=2.64, 95%CI: 1.20-5.81) compared with those with C677T C allele and A1298C A/A genotypes among males. On the contrary, individuals who had C677T T/T and A1298C A/A genotypes were at an decreased risk of developing rectal cancer (adjusted OR=0.47, 95%CI: 0.22-1.03). Conclusions: These results in the present study suggested that polymorphisms of the MTHFR C677T could influence susceptibility to colon or rectal cancer and that there was a coordinated effect between MTHFR A1298C A/A and C677T T/T genotypes among males.

Key Words: Colorectal cancer - methylenetetrahydrofolate reductase - genomic polymorphism

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Introduction

The 5,10-methylenetetrahydrofolate reductase (MTHFR) enzyme plays an important role in folate metabolism and determines the balance between the different forms of folate for DNA synthesis and DNA methylation (Bailey et al, 1999; Fodinger et al, 2000). MTHFR catalyzes the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a substrate for the conversion of homocysteine to methionine. The latter is a precursor to S-adenosylmethionine, which is an important methyl donor for DNA methylation. In addition, 5,10-methylene-tetrahydrofolate, a substrate of MTHFR, is also required for thymidylate and purine synthesis.

Folate derivatives are essential for normal synthesis and methylation of DNA. Therefore, folate deficiency may be related to carcinogenesis though a disturbance of DNA methylation. Not surprisingly, polymorphisms in genes related to folate metabolism, specifically MTHFR, are thought to play a role in carcinogenesis of the large bowel. Two polymorphisms in the MTHFR gene that affect the efficiency of folate metabolism have been described (Fodinger et al, 2000). The MTHFR 677 C>T transition in exon 4 and MTHFR 1298 A>C transversion in exon 7 are associated with reduced enzyme activity resulting in slower folate metabolism. The MTHFR 677 TT genotype results in 30% enzyme activity in vitro compared with the CC wild-type (Frosst P et al, 1995), whereas the MTHFR 1298 CC genotype has been found to have 60% of the AA wild-type enzyme activity in vitro (Van et al, 1998; Weisberg et al, 1998).

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Our previous studies (Gao et al, 2002; Wu et al, 2002; Gao et al, 2003; Gao et al, 2003; Gao et al, 2004) have shown the relationships between genetic polymorphisms of MTHFR and the susceptibility of stomach and esophageal cancer. To investigate possible relations between genetic polymorphisms of MTHFR and the susceptibility of colorectal cancer, we conducted a case-control study in Jiangsu province, China.

Materials and Methods

Study subjects

We recruited colorectal cancer cases using data of Cancer Registries in Huian and Jintan Cities of Jiangsu Province of China, and also recruited cases who visited Jiangsu Province Cancer Hospital from these cities from Aug. 2000 to Sept.2002. All were histopathologically diagnosed as having a primary colorectal cancer. Physicians at the hospital asked eligible cases to participate in our study, and doctors or nurses interviewed the subjects and collected blood samples from a peripheral vein after obtaining informed consent. Population-based controls were selected from healthy residents in eight villages or towns of Huian and Jintan Cities. Doctors of the public health center randomly selected one or two controls for each case, after matching for ethnicity, sex and age within 2 years using the records of residents at the local governmental office, and then asked eligible residents for their participation. Interviews and blood collection were performed as for the cancer cases. A few patients and residents refused to participate in our study, but the response rates were 97% for cases and 93% for controls.

Table 1. Age and Sex Distributions of Colorectal Cancer Cases and their Controls

Variables	Controls	Cancer cases		
		Colorectal	Colon	Rectal
Age (years)				
<40	42 (11.3)	44 (14.0)	14 (13.3)	30 (14.3)
40-49	52 (14.0)	54 (17.1)	15 (14.3)	39 (18.6)
50-59	121 (32.6)	88 (27.9)	30 (28.6)	58 (27.6)
60-69	115 (31.0)	85 (27.0)	26 (24.8)	59 (28.1)
>70	41 (11.1)	44 (14.0)	20 (19.1)	24 (11.4)
Total	371 (100)	315 (100)	105 (100)	210 (100)
Mean age	56.1	55.3	56.4	54.7
Sex				
Males	223 (60.0)	190 (60.3)	65 (61.9)	125 (59.5)
Females	148 (40.0)	125 (39.7)	40 (38.1)	85 (40.5)

Note: Comparisons: age distribution in colorectal cancer and controls, χ2MH=5.36, P=0.2519; sex distribution, χ2=0.00, P=0.9555; age distribution in colon cancer and controls, χ2MH=5.87, P=0.2094; sex distribution, χ2=0.11, P=0.7397; age distribution in rectal cancer and controls, χ2MH=4.21, P=0.3786; sex distribution, χ2=0.02, P=0.8903.

The ethics committee of Jiangsu Province Institute of Cancer Research approved this study.

Environmental factors

The items of our questionnaire covered smoking and drinking habits. Smokers were divided into never- and ever-smokers (current and former). Drinkers also were divided into two groups (1 times/week and <1 times/week) according to drinking frequency.

DNA extraction and genotyping of the MTHFR C677T and A1298C

Whole blood was collected into EDTA-coated tubes

Table 2. Distribution of the MTHFR Genotypes in Colorectal Cancers and their Controls

Sex MTHFR genotypes	Controls	Colon cancer	χ2 value	P value	Rectal cancer	χ2 value	P value	Colorectal cancer	χ2 value	P value
Total										
C677T										
C/C	121 (32.7)	30 (28.6)	0.88	0.643	79 (37.6)	2.01	0.366	109 (34.6)	0.37	0.832
C/T	183 (49.5)	53 (50.5)			101 (48.1)			154 (48.9)		
T/T	66 (17.8)	22 (21.0)			30 (14.3)			52 (16.5)		
A1298C										
A/A	239 (64.4)	66 (62.9)	2.26	0.323	138 (65.7)	0.58	0.748	204 (64.8)	2.52	0.284
A/C	119 (32.1)	38 (36.2)			67 (31.9)			105 (33.3)		
C/C	13 (3.5)	1 (0.9)			5 (2.4)			6 (1.9)		
Males										
C677T										
C/C	72 (32.3)	18 (27.7)	3.46	0.178	49 (39.2)	2.82	0.244	67 (35.3)	0.44	0.803
C/T	118 (52.9)	31 (47.7)			64 (51.2)			95 (50.0)		
T/T	33 (14.8)	16 (24.6)			12 (9.6)			28 (14.7)		
A1298C										
A/A	138 (61.9)	39 (60.0)	2.78	0.249	85 (68.0)	1.42	0.492	124 (65.3)	1.80	0.407
A/C	77 (34.5)	25 (38.5)			37 (29.6)			62 (32.6)		
C/C	8 (3.6)	1 (1.5)			3 (2.4)			4 (2.1)		
Females										
C677T										
C/C	49 (33.3)	12 (30.0)	1.73	0.421	30 (35.3)	0.11	0.948	42 (33.6)	0.47	0.789
C/T	65 (44.2)	22 (55.0)			37 (43.5)			59 (47.2)		
T/T	33 (22.5)	6 (15.0)			18 (21.2)			24 (19.2)		
A1298C										
A/A	101 (68.2)	27 (67.5)	1.54	0.464	53 (62.4)	1.31	0.520	80 (64.0)	1.81	0.405
A/C	42 (28.4)	13 (32.5)			30 (35.3)			43 (34.4)		
C/C	5 (3.4)	0 (0.0)			2 (2.4)			2 (1.6)		

and centrifuged for 15 min, and the buffy coat layer was isolated. Genomic DNA was extracted from 200μl of buffy coat using a Qiagen QIAamp DNA Blood Mini Kit (QIAGEN Inc., Valencia, CA). Genomic DNA was isolated from gastric mucosal tissue using QIAamp DNA Mini Kit (Qiagen Inc., Valencia, CA) according to the manufacturer's instructions. MTHFR C677T and A1298C mutations were detected after PCR amplification with the corresponding primers according to our previous studies (Gao et al, 2002; Wu et al, 2002; Gao et al, 2003; Gao et al, 2004) . The restriction enzyme Hinf was used to distinguish the 677 (C/T) polymorphism. The primers were 5'-TGAAGGAGAAG-GTGTCTGCGGGA-3' and 5'-AGGACGGTGCGGTG-AGAGTG-3'. The PCR product was subjected to Hinf I restriction enzyme digestion and samples were then analyzed by electrophoresis in 3% agarose gels stained with ethidium bromide. There were three genotypes of MTHFR C677T: C/C (198 bp); C/T (198 bp/175 bp); T/T (175 bp). The restriction enzyme Mbo was used to distinguish the 1298 (A/C) polymorphism. The primers were 5'-CTTTGGGGAGCTGAAGGACTACTAC-3' and 5'-CACTTTGTGACCATTCCGGTTTG-3'. The PCR product was subjected to Mbo restriction enzyme digestion and samples were then analyzed by electrophoresis in 4% agarose gels stained with ethidium bromide. There were three genotypes of MTHFR A1298C: A/A (56 bp); A/C (56 bp/84 bp); C/C (84 bp).

Statistical analysis

ORs and their 95% confidence intervals (CIs) of all items for cases and controls were estimated for data analyses, using the unconditional logistic regression model. We calculated adjusted ORs for age (continuous), residence, sex, tea consumption, smoking and drinking habits. The procedure LOGISTIC from the statistical package SAS was employed for the calculations. The probability of Hardy-Weinberg equilibrium was assessed by the $\chi 2$ test with the statistical package Epi-info.

Results

Numbers of subjects were 190 male and 125 female cases with colorectal cancer, and 223 male and 216 female controls (Table 1). The proportion of females in controls was significantly higher than in colorectal cases but the mean age did not differ between cases and controls. The proportional distributions of smokers and alcohol drinkers were significant higher in colorectal cancer cases than in controls.

The distribution of the MTHFR C677T and A1298 genotypes or their alleles did not vary significantly between controls and colon cancer or rectal cancer cases (Table 2). For the 677 locus, the frequencies of the CC, CT, and TT genotypes were 32.7%, 49.5%, and 17.8%, respectively, among the control subjects. The corresponding frequencies among the colorectal cancer cases were 34.6%, 48.9%, and 16.5%, respectively. The T allele frequency was 0.43 for cases and 0.41 for controls. For colon cancer cases, the frequencies of the TT genotype (21.0%) and T allele (0.46) were higher than those for control; but for rectal cancer cases, they (14.3% and 0.38) were lower than those for controls. However no significantly different was found. For the 1298 locus, the prevalence of the AA, AC, and CC genotypes was 64.4%, 32.1%, and 3.5%, respectively, among the controls and 64.8%, 33.3%, and 1.9%, respectively, among the cases. The C allele frequency was 0.18 for cases and 0.20 for controls. Whereas for colon or for rectal cancer cases, the frequencies of the CC genotype (0.9% or 2.4%) and C allele (0.19 or 0.18) were lower than those for control, but no significantly different was found. The allelic distributions of the MTHFR polymorphisms of all groups were in Hardy-Weinberg equilibrium ($p>0.05$).

Table 3. MTHFR Genotypes and Risk of Colorectal Cancer

Sex/MTHFR genotypes	Colon OR (95%CI)	Rectal OR (95%CI)	Colorectal OR (95%CI)
Total			
C677T			
C/C	1.00	1.00	1.00
C/T	1.18 (0.71-1.96)	0.85 (0.58-1.25)	0.94 (0.67-1.32)
T/T	1.16 (0.84-1.59)	0.79 (0.60-1.03)	0.91 (0.72-1.14)
C/C+C/T	1.00	1.00	1.00
T/T	1.28 (0.74-2.22)	0.75 (0.46-1.21)	0.91 (0.60-1.36)
A1298C			
A/A	1.00	1.00	1.00
A/C	1.12 (0.70-1.78)	0.94 (0.65-1.36)	1.01 (0.73-1.40)
C/C	0.51 (0.18-1.44)	0.81 (0.48-1.38)	0.73 (0.45-1.21)
A/C+C/C	1.04 (0.66-1.64)	0.91 (0.63-1.31)	0.97 (0.70-1.33)
Males			
C677T			
C/C	1.00	1.00	1.00
C/T	1.09 (0.56-2.14)	0.84 (0.52-1.37)	0.90 (0.58-1.40)
T/T	1.39 (0.92-2.08)	0.70 (0.47-1.04)	0.94 (0.68-1.28)
C/C+C/T	1.00	1.00	1.00
T/T	2.15 (1.07-4.33)	0.60 (0.29-1.24)	1.05 (0.60-1.84)
A1298C			
A/A	1.00	1.00	1.00
A/C	1.06 (0.59-1.92)	0.73 (0.45-1.19)	0.85 (0.56-1.30)
C/C	0.65 (0.22-1.89)	0.76 (0.38-1.53)	0.75 (0.40-1.40)
A/C+C/C	1.01 (0.57-1.80)	0.71 (0.44-1.14)	0.82 (0.54-1.25)
Females			
C677T			
C/C	1.00	1.00	1.00
C/T	1.47 (0.65-3.36)	0.95 (0.51-1.75)	1.10 (0.63-1.91)
T/T	0.98 (0.55-1.74)	0.85 (0.57-1.26)	0.89 (0.62-1.27)
C/C+C/T	1.00	1.00	1.00
T/T	0.65 (0.25-1.72)	0.85 (0.44-1.65)	0.78 (0.43-1.42)
A1298C			
A/A	1.00	1.00	1.00
A/C	1.21 (0.56-2.60)	1.32 (0.73-2.36)	1.31 (0.77-2.21)
C/C	---	0.84 (0.35-1.99)	0.67 (0.29-1.56)
A/C+C/C	1.04 (0.49-2.23)	1.25 (0.71-2.21)	1.21 (0.73-2.01)

Note: ORs are adjusted by age, residence, smoking, alcohol drinking and tea consumption

When men and women were assessed together, No significant relation was observed between MTHFR C677T or A1298C polymorphisms and colon or rectal cancer susceptibility (Table 3). Furthermore, we analyses the relation between MTHFR polymorphisms and colorectal cancer susceptibility among different sexes. Among males, individuals who had MTHFR C677T T/T genotype were at a significantly higher risk of developing colon cancer (age-, residence-, smoking, alcohol drinking-, tea consumption-adjusted OR=2.15, 95%CI: 1.07-4.33) compared with those who had C677T C allele. No significant relation was observed between MTHFR

Table 4. Interactions between MTHFR C677T and A1298C Polymorphisms and the Risk of Colorectal Cancer

Genotypes		Controls	Colon cancer			Rectal cancer			Colorectal cancer		
C677T	A1298C	(n)	n	OR	95%CI	n	OR	95%CI	n	OR	95%CI
Total											
C/C+C/T	A/A	175	44	1.00		109	1.00		153	1.00	
C/C+C/T	A/C+C/C	129	39	1.18	0.72-1.93	71	0.85	0.58-1.25	110	0.95	0.68-1.33
T/T	A/A	63	22	1.45	0.80-2.63	29	0.71	0.42-1.20	51	0.92	0.59-1.43
T/T	A/C+C/C	3	0	---	---	1	0.51	0.05-5.27	1	0.36	0.04-3.66
Males											
C/C+C/T	A/A	106	23	1.00		74	1.00		97	1.00	
C/C+C/T	A/C+C/C	84	26	1.34	0.70-2.57	39	0.63	0.38-1.03	65	0.82	0.53-1.27
T/T	A/A	32	16	2.64	1.20-5.81	11	0.47	0.22-1.03	27	0.99	0.54-1.82
T/T	A/C+C/C	1	0	---	---	1	1.06	0.06-18.92	1	0.83	0.05-14.7
Females											
C/C+C/T	A/A	69	21	1.00		35	1.00		56	1.00	
C/C+C/T	A/C+C/C	45	13	0.96	0.43-2.17	32	1.35	0.72-2.52	45	1.23	0.71-2.14
T/T	A/A	31	6	0.66	0.24-1.84	18	1.03	0.49-2.17	24	0.90	0.46-1.76
T/T	A/C+C/C	2	0	---	---	0	---	---	0	---	---

Note: ORs are adjusted for age, residence, smoking, alcohol drinking and tea consumption

Table 5. Multivariate Analyzes of Genotypes of MTHFR and Colorectal Cancer

Item		Colon cancer		Rectal cancer		Colorectal cancer	
		OR	95%CI	OR	95%CI	OR	95%CI
Total							
C677T	T/T vs.C/C+C/T	1.34	0.75-2.40	0.70	0.42-1.15	0.88	0.58-1.35
A1298C	A/C+C/C vs.A/A	1.12	0.69-1.82	0.84	0.58-1.22	0.93	0.67-1.31
Smoking	yes vs.no	0.83	0.48-1.42	1.02	0.66-1.58	0.97	0.66-1.41
Alcohol drinking	yes vs.no	1.56	0.89-2.74	2.09	1.35-3.25	1.90	1.28-2.82
Tea drinking	yes vs.no	0.85	0.51-1.39	0.83	0.56-1.23	0.82	0.58-1.17
Males							
C677T	T/T vs.C/C+C/T	2.42	1.13-5.18	0.52	0.25-1.08	0.97	0.54-1.74
A1298C	A/C+C/C vs.A/A	1.30	0.69-2.45	0.64	0.39-1.04	0.82	0.53-1.26
Smoking	yes vs.no	0.70	0.37-1.31	1.08	0.65-1.79	0.95	0.61-1.47
Alcohol drinking	yes vs.no	2.07	1.10-3.89	2.56	1.55-4.20	2.33	1.50-3.60
Tea drinking	yes vs.no	0.98	0.53-1.82	0.84	0.52-1.37	0.88	0.57-1.35
Females							
C677T	T/T vs.C/C+C/T	0.64	0.23-1.73	0.92	0.45-1.87	0.82	0.43-1.55
A1298C	A/C+C/C vs.A/A	0.92	0.42-2.03	1.21	0.66-2.23	1.13	0.66-1.95
Smoking	yes vs.no	1.61	0.50-5.18	0.85	0.32-2.25	1.02	0.44-2.34
Alcohol drinking	yes vs.no	0.19	0.02-1.86	1.11	0.38-3.26	0.76	0.28-2.12
Tea drinking	yes vs.no	0.69	0.25-1.87	0.72	0.35-1.47	0.72	0.38-1.36

Note: Logistic regression model included age, residence, smoking, alcohol drinking, tea consumption and genotypes of the MTHFR C677T and A1298C

A1298C polymorphisms and colon or rectal cancer susceptibility among males or females.

Individuals who had C677T T/T and A1298C A/A genotypes were at an increased risk of developing colon cancer (adjusted OR=2.64, 95%CI: 1.20-5.81) compared with those with C677T C allele and A1298C A/A genotypes among males (Table 4). On the contrary, individuals who had C677T T/T and A1298C A/A genotypes were at a decreased risk of developing rectal cancer (adjusted OR=0.47, 95%CI: 0.22-1.03).

The multivariate analyzes of MTHFR and colorectal cancer was showed in table 5. We calculated adjusted ORs for age (continuous), residence, sex, MTHFR C677T or A1298C polymorphisms, tea consumption, smoking and drinking habits. In males, among MTHFR C677T T/T genotype carriers, the OR for colon cancer was 2.42 (95%CI: 1.13-5.18), but the OR for rectal cancer was 2.42 (95%CI: 1.13-5.18). In males, individuals with habit of drinking had a significant higher risk for colon or rectal cancer. No significant relation was observed between MTHFR A1298C polymorphisms or smoking habits or tea consumption and colon or rectal cancer susceptibility.

Discussion

Aberration of genomic DNA methylation may have association with the cell excess hyperplasia. It was showed that genomic DNA methylation, especially methylation of related gene point, could regulate gene expression. The related gene transcription level increased when deminished methylation. Some researchers found that special protooncogenes such as c-Ha-ras gene and c-ki-ras gene were hypomethylation when universal DNA methylation in colorectal adenomas (8%) and colorectal cancer (10%) was lower than in normal mucous membrane (Zhang et al, 1996). It suggests that the development

colorectal cancer may be associated with DNA hypomethylation. It was showed that in those MTHFRC677T T/T genotype carriers, plasma homocysteine levels increased while the level of 5-methyltetrahydrofolate decreased (Frosst P et al, 1995). Experiment in vitro confirms that DNA from subjects with the T/T MTHFR genotype had a significantly higher methyl group acceptance capacity compared with the C/C MTHFR genotype (Stern et al, 2000). It indicates that MTHFR gene mutation inhibited synthesis of methionine (the methyl donor), then lead to DNA hypomethylation.

Further study showed that only the MTHFRC677T T/T subjects with low levels of folate accounted for the diminished DNA methylation (Friso et al, 2002). This indicates that folate status may affect the function of MTHFR and there have an interaction between dietary factors and MTHFR polymorphism. MTHFR gene mutation caused aberration of DNA methylation, so it may associate with the development of cancer. In this study, when men and women were assessed together, no significant relation was observed between MTHFR C677T or A1298C polymorphisms and colon or rectal cancer susceptibility. But when male and female are separated, men who had MTHFR C677T T/T genotype were at a significantly higher risk of developing colon cancer. Among males, we also found a significant positive interaction between C677T T/T and A1298C A/A genotypes which increased the risk of developing colon cancer and decreased the risk of developing rectal cancer. But no significant relation was observed among females.

There have been a lot of papers on the relation between MTHFR gene polymorphism and colorectal cancer susceptibility (Chen et al, 1996; Ma et al, 1997; Slattery et al, 1999; Ulrich et al, 1999; Park et al, 1999; Jiang et al, 2004). Their results are different when they only analysis the relationship between MTHFR C677T gene polymorphism and colorectal cancer susceptibility, but when combined with the effect of plasma level or dietary intake of folate, methionine, vitamin B6, vitamin B12, and so on, the relation between MTHFR C677T gene polymorphism and colorectal cancer was influenced by these factors. Ma et al (1997) found that men with MTHFR C677T T/T genotype had half the risk of colorectal cancer compared with the C/C or C/T genotypes. Overall, the deficiency of plasma folate levels increased the risk of colorectal cancer among individuals with all genotypes and it was strongest in T/T genotype carriers. Slattery et al (1999) did not get statistically significant results when analyzed the relationship between MTHFR C677T polymorphism and colorectal cancer susceptibility, but in individuals with high levels of intake of folate, vitamin B6, and vitamin B12, MTHFR C677T T/T genotype was protective against the development of colon cancer. Ulrich et al (1999) reported that MTHFR C677T T/T genotype carriers were at a significantly higher risk of developing colorectal adenomas when they had low intakes of folate, vitamin B12, and vitamin B6. We have designed a questionnaire about dietary intake according to the result of epidemiology sampling survey about dietary intake of residents in Jiangsu Province and the case-control study is being conducted. In this paper, we did not analyze the interaction between MTHFR polymorphism and environmental factors especially intake of nutriments with the risk of colorectal cancer. But according to different results of the relationship between MTHFR gene polymorphism and colon, rectal cancer in males and females, there may have an interaction between MTHFR polymorphism and environmental factors associated with the development of colorectal cancer. In China, lifestyle of male and female are different, especially habits of tea consumption, smoking and drinking and these habits were associated with plasma levels of folate and other vitamins of B family.

In this study, we also found that individuals who had MTHFR C677T T/T genotype were at an increased risk of developing colon cancer, but they were at a decreased risk of developing rectal cancer. Kim et al (2004) also studied the relationship between MTHFR gene polymorphism and colon and rectal cancer in Korean. The individuals with MTHFR C677T C/T and T/T genotypes were at an higher risk of developing colon cancer (adjusted OR=2.01, 95% CI£∫1.14-3.53). On the contrary, the risk of rectal cancer was found to be lower in those with the C/T and T/T genotypes combined (adjusted OR= 0.67, 95% CI: 0.43-1.07). It was similar to ours. Slattery et al (2005) found that PPARgamma gene polymorphism had an inverse function on the development of colon cancer and rectal cancer when they studied the association between the PPARgamma gene polymorphism and the risk of colorectal cancer. When they evaluated the associations of genetic polymorphisms in the Insulin, insulin-like growth factor (IGF), and IGF binding protein (IGFBP) genes with colorectal cancer, the data also suggest that the insulin-related pathway may be important in the etiology of colon cancer but not rectal cancer (Slattery et al, 2004). These results indicated that colon cancer and rectal cancer may have different pathogenesis.

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